Reply

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Reply

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Conflicts of interest
None declared.

Manuscript

Dear Sir,

We thank Dr. Saltaji for the interest in our empirical study on the role of historical control groups in orthodontics (1) and for the opportunity to explain our findings, focusing on the main comparison of our study (i.e. historical versus concurrent controls).

First, the concern expressed by Dr. Saltaji is understandable, but not necessarily wholly justified. By careful consideration of the forest plot for the main analysis (Figure 2), it is evident that there is a large variation in effect magnitude of the included meta-analyses, but not in the effect direction of the included meta-analyses (i.e. all black boxes lie on different gray contours, but are always to the left of the central line). Additionally, no statistical heterogeneity can be measured (I^2=0%). Therefore, if this wide array of different interventions and outcomes indicates consistency, this might be expected to contribute to the credibility results. Of course this might be negated in the future by additional meta-analyses with completely opposite effects, but this has always been the case of evolution of evidence in the scientific procedure. However, based on existing evidence, the 95% predictive intervals (2) indicate that we might expect the ΔSMD for historical controls in future meta-analysis to lie between -0.56 and -0.07 (Table 2); therefore it would still be consistent.

Second, Dr. Saltaji correctly identifies the importance of appropriate basic study design, as this might influence both the magnitude (3) and statistical significance (4) of their results. However, this has been taken into account in our study through the use of multivariable regression methods to adjust for meta-confounders (5). To put it plainly, we calculated the influence of the control group on the study results, while at the same time controlling for the confounding effect of the basic study design (i.e. whether the study was prospective and retrospective). The use of this technique enabled calculation of more precise estimates (6); though with the cost of having fewer eligible meta-analyses.

Third, we comprehend the appeal of setting a minimum number of trials per meta-analysis. It must be however made clear, that the number of 5 trials / meta-analysis that is suggested is an arbitrarily set number and that neither the cited Egger et al. (7) study nor the original commentary of Clarke (8), upon which the statement of the former is based, provide any empirical evidence for adopting such a cut-off in this or future meta-epidemiological studies.

Fourth, as originally reported, *post hoc* power analysis with the method recently proposed by Girardeau et al. (9) indicated that 4-7 extra studies would improve statistical power (although this technique does not precisely reflect the multivariable nature of our analysis plan). However, contrary to Dr. Saltaji's statement, there is no evidence whatsoever that the results of our meta-epidemiological study are heterogeneous, as I^2 was 0% and all studies were consistent on their direction.

The plea of Dr. Saltaji for more meta-analyses including clinical trials of interventions with historical control groups to inform future empirical assessments might make sense from an epistemological point of view, but based on existing evidence could be clinical misleading. Given the state of our evidence base (10), every attempt should be made to improve the quality of orthodontic meta-analyses (11) and to safeguard our clinical recommendations from known *or suspected* sources of bias.

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